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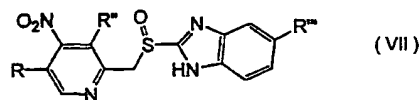
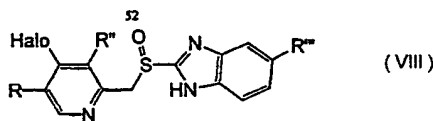
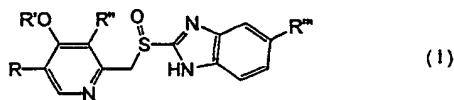
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(54) Title: PROCESS FOR THE PRODUCTION OF 2-(2-PYRIDINYLMETHYLSULPHINYL)-1H-BENZIMIDAZOLES



(57) Abstract: Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphanyl) - 1H-benzimidazole of general formula (I), where R = H or alkyl radical; R' = Alkyl chain, which may or may not be interrupted by an atom of oxygen; R'' = alkyl or alkoxy radical such as methyl and methoxy; R''' = H or alkoxy remnant which may or may not be substituted, characterised in that it is carried out by the replacement of an halogen in position "4" of the pyridine ring of the compounds of general formula (VIII) by an alkoxide in the presence of a base and within an aprotic polar solvent; or by replacement of a "nitro" group in position "4" of the pyridine ring of the compounds of the compounds of formula (XVII) by an alkoxide radical R'O[•] in the presence of a base and within a mixture of solvents made up of the corresponding to alcohol R'OH and another aprotic polar solvent. It is useful for the treatment or prevention of gastric ulcers.

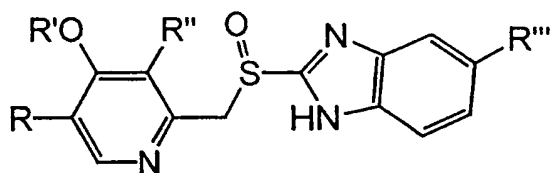
**PROCESS FOR THE PRODUCTION OF
2-(2-PYRIDINYMETHYLSULPHINYL)-1H-BENZIMIDAZOLES**

5

1.- FIELD OF THE INVENTION

This invention relates to a new procedure for making derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I):

10



(I)

15 including their metal or quaternary ammonium salts, such as the corresponding salts of Li, Na, K, Mg, Ca, Ti, N^+R_4 (where R is a C_{1-4} -alkyl radical), in which:

R represents an atom of hydrogen or an alkyl radical such as methyl;

20 R' represents an alkyl chain, which may or may not be interrupted by an atom of oxygen, such as methyl and 3-methoxypropyl;

R'' represents an alkyl or alkoxy radical such as methyl and methoxy;

25 R''' represents an atom of hydrogen or an alkoxy remnant which may or may not be replaced, such as methoxy and difluoromethoxy.

The new procedure permits these compounds to be
30 obtained, which compounds possess gastric acid secretion

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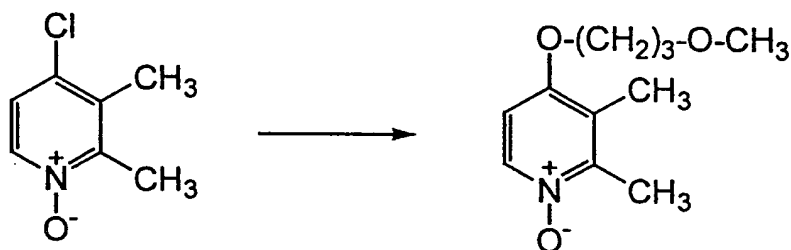
inhibiting properties and are therefore used in the treatment or prevention of peptic ulcers, in an advantageous manner in relation to other methods, from both the economic and technical viewpoints.

5

2.- BACKGROUND OF THE INVENTION

The compounds of this invention of general formula (I) are known and possess common international 10 denominations such as omeprazol (R, R' and R'' = -CH₃; R''' = OCH₃, rabeprazol or pariprazol (R and R''' = H; R' = CH₃-O (CH₂)₃-; R'' = CH₃) and pantoprazol (R = H; R' = -CH₃; R'' = -OCH₃; R''' = -OCF₂), long and costly processes of synthesis on the basis of the commercially available raw materials 15 having so far been necessary.

Thus, for example, in Eidepean Patent EP 268.956 from Eisai, with application date 13 Nov 1987, a process of synthesis of rabeprazol is described in which the 3-methoxypropanolic chain is introduced in position "4" of 20 the chlorated intermediate pyridine ring in the same position, according to the schema:



25 This intermediate is in its turn converted through successive reactions in a thioether derived from 2-benzimidazole which is finally oxidised to the corresponding sulfoxide (1). This method of synthesis presents various disadvantages. Firstly, nine stages of

synthesis are needed to obtain the end product, which has a negative effect on the overall yield of the process. This can be found on the basis of the yields outlined for each one of the intermediates described in said patent and 5 indicated below:

- Obtaining of the *N*-oxide of 4-(3-methoxypropoxy)-2,3-dimethylpyridin: 18.9%;
- Obtaining of 2-acetoxymethyl-4-(3-methoxypropoxy)-3-methylpyridin: 76.8%;
- 10 - Obtaining of 2-hydroxymethyl-4-(3-methoxypropoxy)-methylpyridine: 76.9%;
- Obtaining of 2-chloromethyl-4-(3-methoxypropoxy)-methylpyridine: 96.2%;
- Obtaining of the initial intermediate sulphide for 15 preparing Rabeprazol: 92%.
- Obtaining of rabeprazol: 79.7%.
- Obtaining of sodium salt of rabeprazol: 95.3%.

In accordance with these figures, the overall yield 20 would be 7.5%, while it should also be borne in mind that the yield of the first intermediate indicated is still missing and that obtaining it requires several more additional synthesis steps.

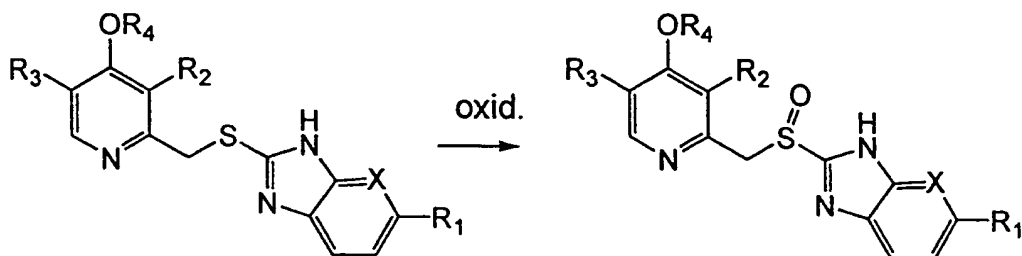
In accordance with these figures, the overall yield 25 would be 7.5%, while it should also be borne in mind that the yield of the first intermediate indicated is still missing and that obtaining it requires several more additional synthesis steps.

Furthermore, the reaction with a high-priced reagent 30 such as 3-methoxypropanol in the first synthesis stages gives rise to an expensive intermediate, which has a negative effect on the cost of the final product due to the successive losses of yield that arise in the subsequent steps of synthesis.

35 Another disadvantage of this process lies in the

habitual formation of impurities in the form of *N*-oxide and sulphone as reaction by-products when the last phase of oxidation of the corresponding sulphide to sulfoxide takes place, given that these last products are easily oxidisable. These sulphonic derivatives are also difficult to eliminate by the usual purification methods such as recrystallisation, due to the formation of mixed crystals with the sulfoxides, as described by F.G. Bordwell in A.C.S., 79, 717 (1957), so that it is sometimes necessary to have recourse to chromatographic methods to separate them, which is very costly. In order to control this problem of exact control of oxidisation, transition metals such as vanadium (Eidepean patent EP 302.720) have been used as catalysts of said reaction and have given good results in terms of reducing the quantity of *N*-oxide but not that of the sulphone, while to this is added the problem of the toxicity of these metals in the active ingredient, since they are used in the last stage of synthesis.

The same problem of the formation of impurities in the form of *N*-oxide and sulphone as by-products of reaction in the oxidisation of sulphur to sulphone arises in the procedures for the preparation of Omeprazol, Lansoprazol and Rabeprazol described in Spanish patent application ES 2036948 from Centro Génesis dated 21 Nov 1991. In Patent Application ES 2026716 from Centro Génesis dated 31 Oct 1990, equivalent to Eidepean patent EP 484265 the obtaining of Omeprazol by such a procedure is claimed explicitly. The final stage common to all the procedures in said Spanish application consists in an oxidisation of the corresponding thioether derived from the 2-benzimidazol to the corresponding bisulphoxide, as indicated in the diagram below:



This procedure means that the chain in position "4" of the pyridine ring has been introduced in some prior stage 5 of the procedure.

In order to resolve this problem of exact control of oxidisation, transition metals such as vanadium (Eidepean patent EP 302.720) have been used as catalysts of said 10 reaction and have given good results in terms of reducing the quantity of *N*-oxide but not that of the sulphone, while to this is added the problem of the toxicity of these metals in the active ingredient, since they are used in the last stage of synthesis.

15 Other oxidising agents used in an attempt to resolve this problem have been, for example, 3-chloroperoxybenzoic acid (WO 91/18895, EP 533752, US 5386032 and EP 484265), magnesium monoperoxyphthalate (EP 533264 and US 5391752), ammonium molybdate (EP 484265), iodosobenzene (ES 539793), 20 methylosobenzene (ES 540147) and sodium peryodate (ES 550070), though without achieving completely satisfactory results either, and making the process more expensive.

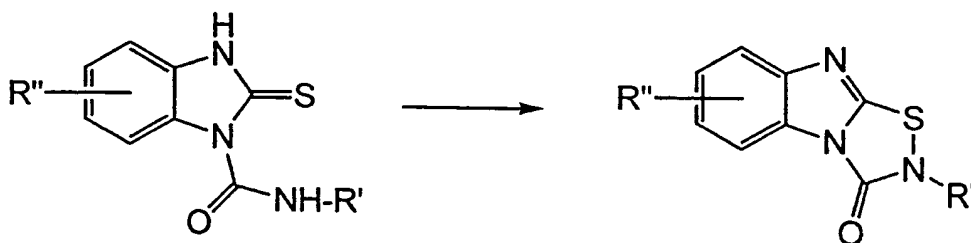
The example most directly related with this last is exemplified in patent application WO 99/02521 dated 10 Jul 25 1998 from Eisai Co., in which a process for preparation of this same type of compounds of general formula (I) is described, including rabeprazol, omeprazol and lansoprazol which consists in oxidisation of the sulphide derivative used as precursor with a peroxoborate salt in the presence

of an anhydride or a catalysing metal with *N*-halosuccinimide, 1,3-dihalo-5,-dimethylhydantoin or with a salt of dichloroisocyanuric acid in the presence of a base. But this does not solve the main problems already
 5 noted of oxidation in the last stage of synthesis, while the process is also made more expensive by the use of these new reagents which are more expensive than the usual ones.

Rather more recently, the firm Knoll claimed in
 10 patent WO 99/47514 a method of oxidation of the sulphoderivative with sodium perborate.

Other patents which describe new processes for preparing this type of compounds are WO 98/40378 with priority date 7 Mar 1997 and WO 98/40377 from Bristol-
 15 Myers, consisting in the prior cyclisation of intermediates of 2,3-dihydro-2-thioxo-1*H*-benzimidazole-1-carboxamide to give rise to 1,2,4-thiadazole [4,5-*a*] benzimidazole -3(2*H*)-one, according to the following synthesis schema:

20



25 This last product is in its turn oxidised to the corresponding 1,2,4-thiadiazole [4,5-*a*] benzimidazole-3(2*H*)-one-1-oxyde which is made to react with the corresponding derivative of *N*-oxide of 2-methylpyridin to produce *N*-oxide sulfoxide and that must finally be
 30 reduced to the end pyridine of general formula (I). This

process also has the disadvantage of the large number of stages of synthesis and the increased cost of the intermediate compounds, in addition to the need to reduce the *N*-oxide resulting from the last stage.

5 In the patent application WO 98/21201 from Takeda dated 13 Nov 1997 a procedure is claimed basically for preparing omeprazol, lansoprazol, pantoprazol, rabeprazol and other homologous products in a solvent-free crystalline form by means of treatment of a solvate of the
10 compound or of its salt for the elimination of same. Also in this reaction the radical of position "4" of the pyridine ring is introduced in phases very much earlier than that of the final oxidisation, suffering from the same defects as the previous processes.

15 In the patent applications from Astra Ak, WO 96/02535 dated 5 Jul 1995 and WO 97/02261 dated 29 Jun 1996, a process is claimed for enantioselective synthesis of these same compounds using an oxidising agent in the presence of a chiral complex of titanium in the last step of synthesis
20 and a process of optical purification for enantiomerically enriched preparations thereof, respectively, for which reasons the same problems are indicated above continue to exist.

Other procedures claimed for the preparation of these
25 compounds of general formula (I) are indicated in patent application WO 97/29103 dated 5 February 1997 from PDI Research Lab., on the basis of a number of \downarrow -ketoalkylyden derivatives as precursors of 1,4-dihydropyridines which are in turn converted by means of oxidisation into the
30 corresponding intermediate pyridines already known and which give rise to the benzimidazolic derivatives by the usual methods. The high number of synthesis steps, the high price of the new reagents, the complexity of making the initial non-commercial intermediates and the need to
35 introduce the position "4" chain of the pyridine ring into

the first intermediates are the main problems this method presents.

Spanish patent ES 2023609 with application date 21 November 1990, from Inke/Química Sintética, S.A. claims a process for obtaining lansoprazol in which this product is prepared by reaction of the corresponding intermediate sulphinyl derivative which it possesses in position "4" of the pyridine ring with a nitro or halogen remnant, with the sodium salt of 2,2,2-trifluoroethanol. More specifically, in said patent the 2-[[3-methyl-4-bromo-2-pyridinyl)methyl] sulphinyl]-1H-benzimidazole is made to react with 2,2,2-trifluoroethanol in pyridine, using K₂CO₃ as base and at a temperature of 80°C for two days. It has been found that in the specific cases of formation of rabeprazol and omeprazol, upon attempting to carry out that same reaction with the sodium salt of the 3-methoxypropanol or with sodium methoxide, respectively, under those conditions the reaction does not occur, since the alcohol proton of the 3-methoxypropanol or the methanol are not sufficiently acid to be able to form the corresponding alkoxy of K₂CO₃, so that these reaction conditions are not applicable to the synthesis of rabeprazol.

That same patent also describes other conditions which consist in making the corresponding 4-nitrosulphoxyde derivative react in place of the 4-halogen derivative, specifically 2-[[3-methyl-4-nitro-2-pyridinyl)methyl] sulphinyl]-1H-benzimidazole with 2,2,2-trifluoroethanol at 77-80° for 20 hours and using potassium butoxide as base. But when an attempt is made to carry out this same reaction with the sodium salt of 3-methoxypropanol under these conditions, we find that complete decomposition of the product takes place, so that these conditions are not applicable either to the manufacturing of rabeprazol or the manufacturing of

omeprazol.

The same occurs with the patent applications from Techquim Establ. ES 2037608 and ES 2037609, with application date 2 Dec 1991 and with ES 2060541 of 5 Laboratorios Viñas with application date 26 Feb 1993, in which only the obtaining of Lansoprazol is claimed.

To sum up, then, we can state that the difference between the basicities of the anions corresponding to the sodium salts of 2,2,2-trifluoroethanol and 3-10 methoxypropanol means that the conditions described for preparing lansoprazol are not applicable to the preparation of rabeprazol.

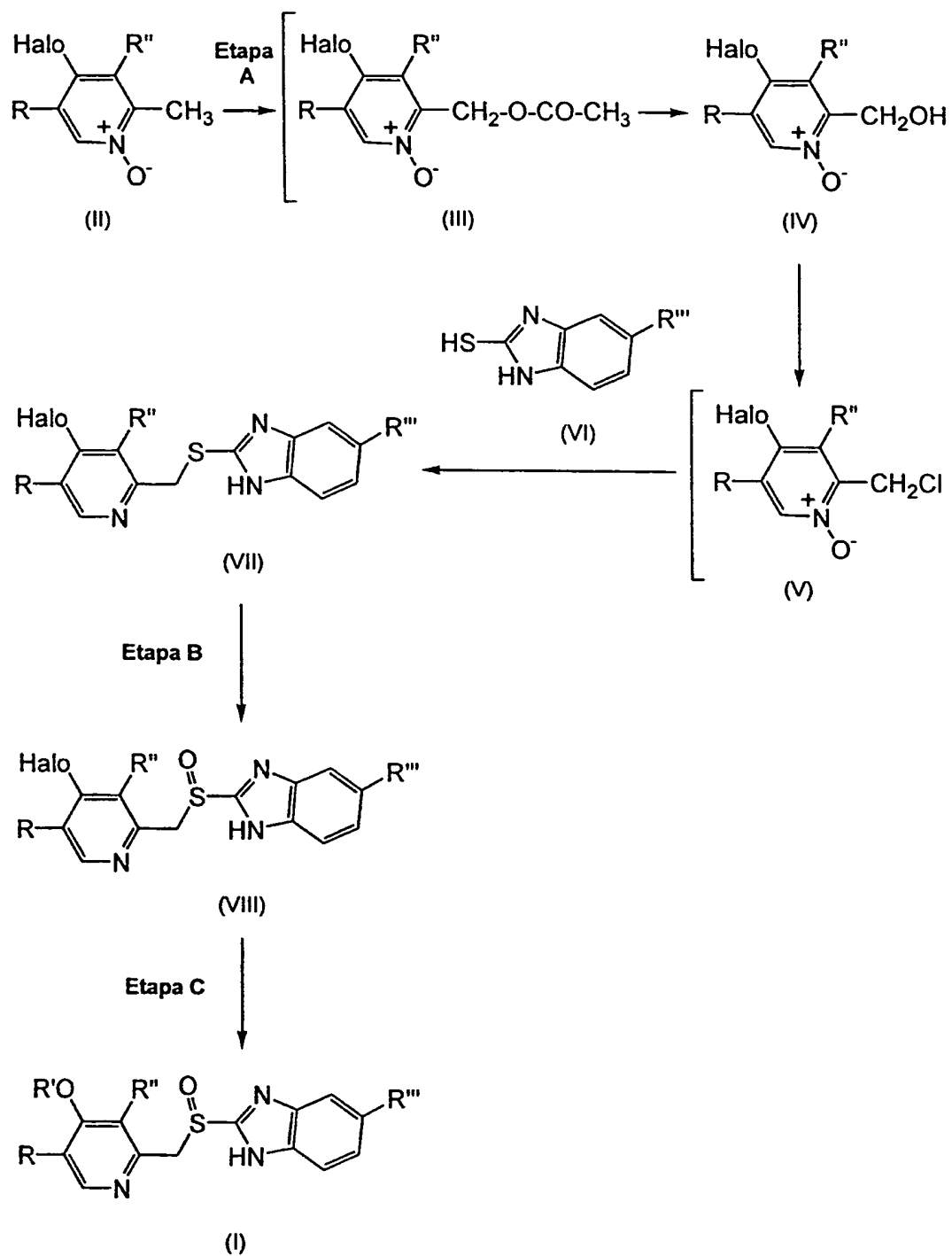
From all this it can therefore be deduced that it remains necessary in this field to seek out alternative 15 synthesis procedures for the compounds of general formula (I) which make it possible to achieve cheaper procedures that are easily industrialisable and that give rise to the least possible quantity of by-products.

Surprisingly, we have found that we can obtain 20 compounds of this type using techniques that simplify the overall process and that, moreover, by means of a new procedure and using certain conditions not described in the bibliography, we succeed in making the final compound of general formula (I) remain stable under the reaction 25 conditions, thereby obtaining products of a high degree of purity and with high yields.

3.- DESCRIPTION OF THE INVENTION

30 This invention relates to a new procedure for the preparation of derivatives of 2-(2-pyridinilmethylsulphonyl) - 1H-benzimidazole of general formula (I), in accordance with the following synthesis schema:

10



including their metal or quaternary ammonium salts, such as the corresponding salts of Li, Na, K, Mg, Ca, Ti, NR_4 (where R is a C_{1-4} -alkyl radical), in which

- 5 - R represents an atom of hydrogen or an alkyl radical such as methyl;
- R' represents an alkyl chain, which may or may not be interrupted by an atom of oxygen, such as methyl and 3-methoxypropyl;
10 - R'' represents an alkyl or alkoxy radical such as methyl and methoxy;
- R''' represents an atom of hydrogen or an alkoxy remnant which may or may not be replaced, such as methoxy and difluoromethoxy.
15 - Halo represents an atom of halogen such as F, Cl, Br or I.

The process of this invention consists in a sequence of reactions summed up in the three phases A, B and C indicated in the above schema.

- 20 Stage A takes place in such a way that the intermediates of general formula (III), (IV) and (V) are obtained "in situ" without isolating or purifying, with the consequent saving of time, energy and equipment occupation.

- 25 Said stage consists in making the 5-R'''-2-(4-halo-5-R-3-R''-2-pyridinyl)methyl]thio]-benzimidazole of general formula (VII) from the corresponding N-oxide of 4-halo-2-methyl-5-R-3-R''-pyridine of general formula (II), obtained previously by known procedures already described in the
30 bibliography.

The intermediate compound 4-halo-5-R-3-R''-2-acetoxymethylpyridine of general formula (III) is made by reaction between the corresponding N-oxide of 4-halo-2-methyl-5-R-3-R''-pyridine of general formula (II) and an
35 anhydride or chloride of alkyl such as acetyl,

trichloroacetyl or trifluoroacetyl, preferably acetic anhydride, in an aprotic solvent such as acetonitril, benzene, chloroform, methylene chloride, dimethylformamide, dimethylsulphoxide, dioxane, 5 methylethylketone, N-methylpyrrolidone, pyridine, carbon tetrachloride, tetrahydrofuran, toluene or xylene, preferably toluene or methylene chloride. The process is carried out at temperatures between ambient temperature and 150°C, preferably between 90-110°C. the reaction time 10 varies between 1 and 10 hours and, once the reaction has been completed the solvent is eliminated by means of evaporation at low pressure and the residue obtained is used just as it is and without further purification is the following stage of synthesis.

15 The intermediate compound 4-halo-5-R-3-R"-2-hydroxymethylpyridine of general formula (IV) is made by basic hydrolysis of the compound 4-halo-5-R-3-R"-2-acetoxymethylpyridine of general formula (III) obtained in the previous phase. The reaction is carried out in a polar 20 solvent such as water, methanol, ethanol, isopropanol and N-butanol, preferably methanol. The base used can be inorganic, such as sodium hydroxide, potassium hydroxide, potassium carbonate, ammonium hydroxide, or organic, such as *terc*-potassium butoxide, preferably potassium 25 hydroxide. The process is carried out at temperatures between ambient temperature and -20 and 80°C, preferably between -5 and 30°C. The reaction time varies between 1 and 14 hours and, once the reaction has been completed the solvent is evaporated at low pressure and the product is 30 extracted from the aqueous phase with an organic solvent such as methylene chloride, chloroform, ethyl ether, *terc*-butylmethyl ether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably methylene chloride, thereby providing a solution of the aforesaid product in 35 an organic solvent which is used just as it is in the

following stage of synthesis.

The intermediate compound 4-halo-5-R-3-R''-2-chloromethylpyridine of general formula (V) is made by reaction between the 4-halo-5-R-3-R''-2-hydroxymethylpyridine of general formula (IV) obtained in the previous phase and a halogenating agent such as the halides of thionyl or the trihalides of phosphorus, preferably thionyl chloride. The reaction can be carried out in an aprotic solvent such as such as acetonitril, benzene, chloroform, methylene chloride, dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, N-methylpyrrolidone, pyridine, carbon tetrachloride, tetrahydrofuran, toluene or xylene, preferably methylene chloride or carbon tetrachloride. The reaction temperature at which the process takes place is between -10°C and the reflux temperature of the solvent, preferably between -15 and 30°C. The reaction time varies between 2 and 12 hours, to provide a solution of 2-chloromethyl pyridine of general formula (V) by means of neutralisation of the reaction mixture with a base such as sodium hydroxide, potassium hydroxide or ammonium hydroxide and subsequent extraction with a water-immiscible solvent such as methylene chloride, chloroform, ethyl ether, terc-butylmethyl ether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably methylene chloride. This solution of the product thereby prepared is used just as it is in the following stage of synthesis.

The final compound obtained from stage A, 5-R''' 2-[[4-halo-5-R-3-R''-2-pyridinyl)methyl]thio-1H-benzimidazole of general formula (VII) is made by condensation between the 4-halo-5-R-3-R''-2-chloromethyl pyridine of general formula (V) obtained in the previous stage and the corresponding 5-R'''-2-mercaptobenzimidazole of general formula (VI), which is now available commercially or can

be prepared in advance by usual known procedures described in the bibliography.

This reaction takes place advantageously when carried out under liquid-liquid phase transfer conditions, using an inorganic base such as sodium hydroxide or potassium hydroxide and phase-transfer catalyst which can belong to the types of quaternary ammonium $R_4N^+X^-$ salts, phosphonium $R_4P^+X^-$ salts, crown and kryptane ethers, polyethylene glycol ethers or amino ethers, phosphorimides or oxyphosphorated or sulphonyl derivatives, preferably quaternary ammonium salts such as the salts of triethylbenzylammonium, tetraethylammonium, tetrabutylammonium, tetraheptylammonium, trioctylmethylammonium (Aliquat 336) and can be the associated X^- anion chloride, bromide, iodide, hydrogen sulphate, arsenate, naphthalenesulphonate, preferably triethylbenzylammonium chloride. The organic phase is constituted by the dissolution of the 4-halo-5-R-3-R''-2-chloromethyl pyridine of general formula (V) obtained in the previous stage. The process can be carried out at temperatures between 0°C and 100°C, preferably between 15 and 30°C, and the reaction time varies between 1 and 10 hours. Once the reaction has finished, the product is isolated by means of concentration and crystallisation.

This same reaction can also be carried out naturally by means of the usual techniques in homogeneous phase and non-transfer of phase, using a polar solvent such as water, methanol, ethanol, isopropanol, n-butanol, acetonitrile or methylsobutylketone, in which there has been prior formation of the salt of the corresponding 5-R'''-2-mercaptobenzimidazole of general formula (VI) and it is made to react with the 4-Halo-5-R-3-R''-2-chloromethylpyridine of general formula (V), which in this case would have been isolated previously from the solution obtained in the previous stage.

Stage B consists in an oxidation reaction of the compound obtained in stage A, 5-R''' 2-[[4-halo-5-R-3-R''-2-pyridinyl)methyl)thio-1H-benzimidazole of general formula (VII) to provide the corresponding 5-R''' 2-[[4-halo-5-R-3-R''-2-pyridinyl)methyl)sulphinyl]-1H-benzimidazole of general formula (VII). The great advantage of this procedure lies in the fact that the oxidation reaction takes place in the penultimate state of synthesis, thereby increasing the possibility of reducing the proportion of 10 N-oxide and sulphone impurities usual in this type of reactions and reducing their percentage in the end product, which must be obtained from this product.

This oxidation can be carried out using various types 15 of reagents already described in the bibliography and commonly used in the oxidation of sulphides to sulphoxides, such as those listed by Madesclaire et al., in Tetrahedron, **42**, 5459 (1986), or also, for example, metachloroperbenzoic acid (Uchida et al., Chem. Pharm. 20 Bull., 38, 534, (1990)), sodium metaperyodate (ES 550070), iodosobenzene (ES 539793), oxygenated water with catalysts of vanadium, titanium or molybdenum (EP 302720) or dioxyranes such as potassium peroxymonosulphate or those generated from ketones and this last reagent (ES 2060541). 25 Any of these agents can be used in the oxidation of intermediate sulphides of general formula (VII) to sulphoxides of general formula (VIII). Nevertheless, the inventors have found that the oxidising agent whose use presents most advantages and is therefore preferably used 30 is peracetic acid, given that surprisingly, in addition to being a very affordable reagent, gives rise in use to the formation of very few by-products, which permits isolation of a final sulphoxide with very low content of N-oxide and sulphone impurities, probably due to mixed crystals not 35 being formed. Moreover, it has also been found that using

a reaction medium made up of a mixture of a halogenated solvent such as chloroform, methylene chloride, dichloroethane, trichloroethane or carbon tetrachloride and an alcohol such as methanol, ethanol, isopropanol, N-propanol, n-butanol or terc-butanol, preferably methylene chloride-isopropanol, largely prevents formation of the impurity sulphone. The process is carried out at temperatures between 0°C and 70°C, preferably between 20 and 25°C, which also prevents formation of the undesirable impurities already indicated. The reaction time varies between 5 minutes following the addition of the peracetic acid and 8 hours. Once the reaction has finished, the halogenated solvent is evaporated at low pressure and the product is crystallised by the addition of water and cooling, for subsequent filtering and purification thereof.

Stage C consists in the nucleophilic substitution of the "halo" radical of the compound obtained in Stage B above,

$$5-R'' \quad 2-[[4\text{-halo-}5-R\text{-}3-R''\text{-}2\text{-pyridinyl)methyl)sulphinyl}]\text{-}1H\text{-benzimidazole}$$

of general formula (VII) by the corresponding alcohol, using certain conditions so that there is no decomposition of the end product obtained,

$$5-R'' \quad 2-[[4\text{-alcoxy-}5-R\text{-}3-R''\text{-}2\text{-pyridinyl)methyl)sulphinyl}]\text{-}1H\text{-benzimidazole}$$

of general formula (I). This reaction takes place in the last stage, which means that the increased cost due to losses through yields are as low as possible where the reagent is expensive, as in the case of the 3-methoxypropanol, since we avoid the progressively greater expense of each one of the intermediates due to the corresponding loss of yield in the successive stages of synthesis if it had been made to reaction in any previous stage. Moreover, this alcohol is not used as a solvent, which is a common practice, which means that the expense involved is reduced still further.

Surprisingly, the authors of this invention have found that when an attempt is made to carry out this reaction under the usual conditions described in the bibliography by replacing a nitro group or a halogen with
5 alcohols such as 3-methoxypropanol instead of 2,2,2-trifluorethanol, as described in Spanish patent ES 2025604 from Inke/Química Sintética, S.A. to make lansoprazol, there takes place either a complete decomposition of the product or there is no reaction at all between the various
10 reagents. This is probably due to the different basicity of the corresponding alkoxides formed "in situ" in order to be able to carry out the aforesaid reaction. This is why the conditions described for lansoprazol in this last patent are not applicable for using it to manufacture
15 rabeprazol.

In the new procedure drawn up in this invention, the reagents and the conditions of temperature, pH, concentration and so forth at which the reaction must be carried out without leading to decomposition of the end
20 product are clearly defined, and include the use of monoethanolamine, triethylamine or other organic base as an agent for stabilising the product in solution.

This substitution reaction is carried out by reaction of the corresponding sodium salt of the reacting alcohol
25 prepared "in situ" by treatment of said alcohol in an aprotic polar solvent such as *N,N*-dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, tetrahydrofuran, diglime, acetonitrile, pyridine, *N*-methylpyrrolidone or the triamide of hexamethylphosphoric
30 acid, preferably *N,N*-dimethylformamide, with a base such as sodium hydride, potassium *tert*-butoxide, metallic sodium, sodium hydroxide, potassium hydroxide or sodium or potassium carbonate or di-isopropylethylamine, preferably sodium hydride, with the 5-R'' 2-[[4-halo-5-R-3-R''-2-
35 pyridinyl)methyl)sulphonyl]-1H-benzimidazole of general

formula (VIII), obtained as indicated in Stage B. The process takes place at temperatures between ambient temperature and 150°C, preferably between 60 and 80°C. Throughout the entire reaction process the pH of the solution has to be between 12.5 and 13.5, adding dilute NaOH or sodium carbonate if necessary, thereby ensuring stability of the product. The reaction time ranges between 1 and 12 hours. Once the reaction has finished the pH of the reaction mixture is adjusted to between 10.8 and 11.0 by the addition of an acid such as acetic acid or hydrochloric acid, preferably acetic acid, and the organic phase is isolated by stabilising it by the addition of monoethanolamine. The aqueous phase, to which has previously been added a small quantity of triethylamine to stabilise it, is extracted with an organic solvent such as methylene chloride, chloroform, ethyl ether, *tert*-butylmethyl ether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably ethyl acetate. Finally, both organic phases are combined, dried and the solvent evaporated at low pressure at a temperature of <40°C. the residue thus obtained is crystallised in the same solvent and is purified by recrystallisation in an organic solvent such as acetonitrile, ethyl acetate, methylethylketone, di-isopropylether, *tert*-butylmethyl ether, *N,N*-dimethylformamide, *n*-hexane, toluene, water-alcohol mixtures or methyl or ethyl formate, preferably acetonitrile.

This invention also relates to a procedure for preparation of derivatives of 2-(2-pyridinylmethylsulphanyl)-1H-benzimidazole of general formula (I), including their metal or quaternary ammonium salts, such as the corresponding salts of Li, Na, K, Mg, Ca, Ti, N^+R_4 (where R is a C₁₋₄-alkyl radical), in which:

R represents an atom of hydrogen or an alkyl radical such

as methyl;

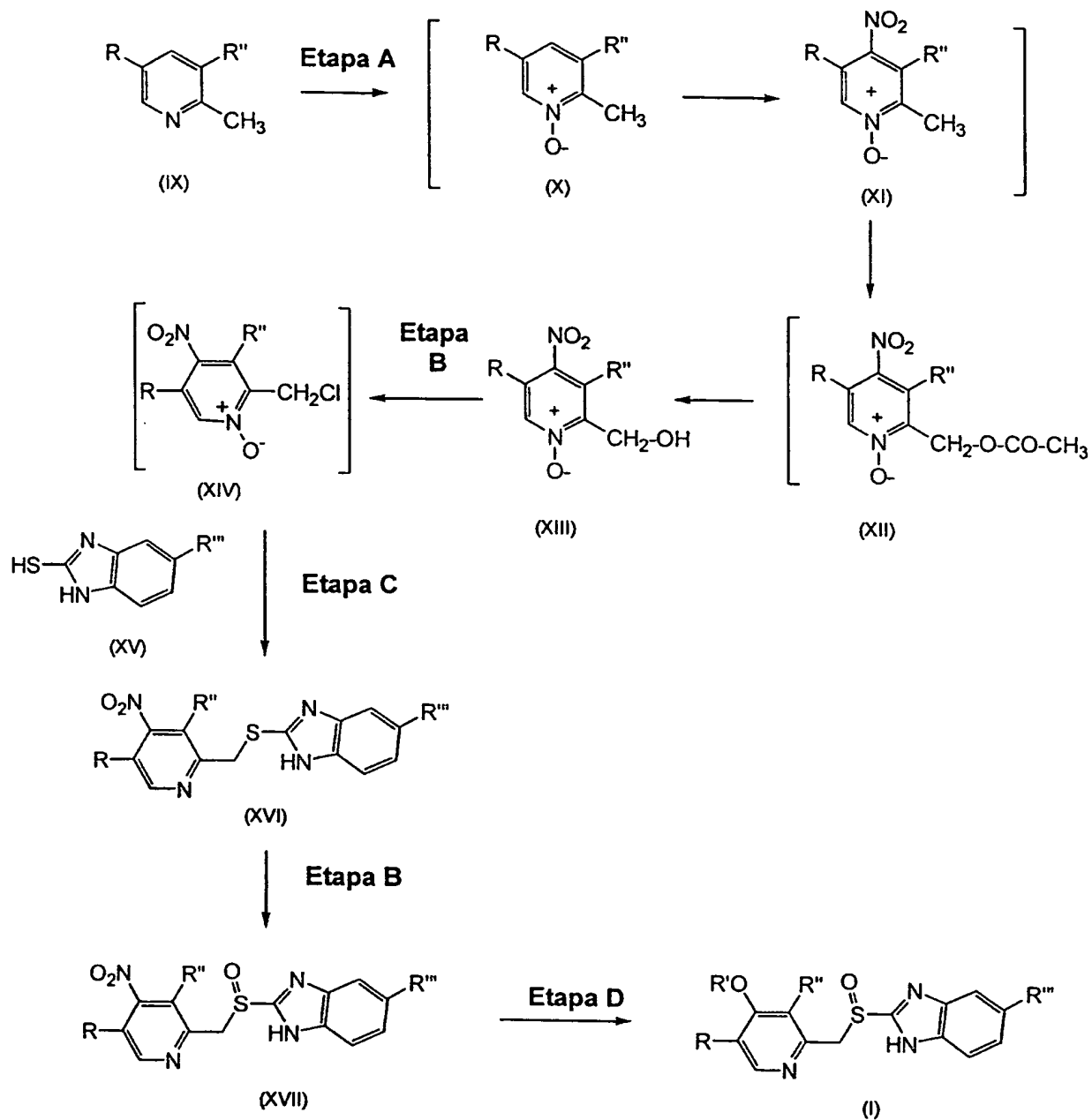
R' represents an alkyl chain, which may or may not be interrupted by an atom of oxygen, such as methyl and 3-methoxypropyl;

5 R'' represents an alkyl or alkoxy radical such as methyl and methoxy;

R''' represents an atom of hydrogen or an alkoxy remnant which may or may not be replaced, such as methoxy and difluoromethoxy,

10 in accordance with the following synthesis scheme:

20



Stage A takes place in such a way that the intermediates of formula (X), (XI) and (XII) are not isolated or purified, but are made to react "in situ" with the consequent saving of time, energy and equipment

occupation.

Said stage consists in making 3-R''-5-R-2-hydroxymethyl-4-nitropyridine of formula (XIII) from the N-oxide of 2-methyl-3-R''-5-R-pyridine de formula (X),
5 obtained previously from the suitable 2-methyl-3-R''-5-R-pyridine (IX), in accordance with known procedures already described in the bibliography, such as oxidation with peracetic acid.

The intermediate N-oxide compound of de 4-nitro-2-
10 methyl-3-R''-5-R-pyridine of formula (XI) is obtained by reaction between the N-oxide of 2-methyl-3-R''-5-R-pyridine of formula (X) and nitric acid, in accordance with the conventional nitration methods described in the bibliography.

15 The intermediate compound of 3-R''-5-R-4-nitro-2-acetoxymethylpyridine of formula (XII) is in turn obtained by reaction between the N-oxide de 4-nitro-2-methyl-3-R''-5-R'-pyridine of formula (XI) and an anhydride or chloride of akyl such as acetyl, trichloroacetyl or
20 trifluoroacetyl, preferably acetic anhydride, in a solvent such as acetonitryl, benzene, chloroform, methylene chloride, dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, N-methylpyrrolidone, pyridine, carbon tetrachloride, tetrahydrofuran, toluene or xylene,
25 preferably in acetic acid. The process is carried out at temperatures between ambient temperature and 150°C, preferably between 60-80°C. The reaction time varies between 2 -10 hours and, once the reaction has terminated the solvent is eliminated by evaporation at reduced
30 pressure and the residue obtained is used just as it is and without further purification in the following stage of synthesis.

The intermediate compound 3-R''-5-R-2-hydroxymethyl-4-nitropyridine of formula (XIII) is obtained by basic
35 hydrolysis of the compound 3-R''-5-R-4-nitro-2-

acetoxymethylpyridine of formula (XII) obtained in the previous stage. The reaction can be carried out in a hydroxylic polar solvent such as water, methanol, ethanol, isopropanol and n-butanol, preferably methanol. The base
5 used can be inorganic such as sodium hydroxide, potassium hydroxide, potassium carbonate, ammonium hydroxide, or inorganic, such as sodium methoxide and potassium *tert*-butoxide, preferably potassium hydroxide or sodium methoxide. The process is carried out at temperatures
10 ranging between -20 and 80°C, preferably between -5 and 30°C. The reaction time varies between ½ and 10 hours and, once the reaction has finished, the solvent is evaporated at low pressure and the product is extracted from the aqueous phase with a organic solvent such as methylene
15 chloride, chloroform, ethyl ether, *tert*-butylmethyl ether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably methylene chloride, thus providing a solution of the indicated product in an organic solvent from which it is later isolated by extracting it with an
20 acid, such as hydrochloric acid, and is finally precipitated at a pH ranging between 7,5-8.

Stage B takes place in such a way that the intermediate 2-Chloromethyl-3-R''-5-R-4-nitropyridine of
25 formula (XIV) is not isolated or purified, but is made to react "in situ", with the consequent saving of time, energy and equipment occupation.

Said stage consists in obtaining 5-R'''-2-[[[3-R''-5-R-4-nitro-2-pyridinyl) methyl]thio]-1*H*-benzimidazole of
30 formula (XVI) from the 3-R''-5-R-2-hydroxymethyl-4-nitropyridine of formula (XIII) obtained in stage A.

The intermediate compound 2-chloromethyl-3-R''-5-R-4-nitropyridine of formula (XIV) is prepared by reaction between the 3-R''-5-R-2-hydroxymethyl-4-nitropyridine of
35 formula (XIII) obtained in the above stage A and a

halogenating agent such as the halides of thionyl or the halides of phosphorus, preferably thionyl chloride. The reaction can be carried out in an aprotic solvent such as acetonitrile, benzene, chloroform, methylene chloride, dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, *N*-methylpyrrolidone, pyridine, carbon tetrachloride, tetrahydrofuran, toluene or xylene, preferably methylene chloride or carbon tetrachloride. The reaction temperature at which the process takes place ranges between -10°C and the reflux temperature of the solvent, preferably between 0-5°C. The reaction time ranges between ½ and 8 hours, providing a solution of 2-chloromethyl pyridine of formula (XIV) by prior neutralisation of the reaction mixture with a base such as sodium hydroxide, potassium hydroxide or ammonium hydroxide and subsequent extraction with a water-immiscible solvent such as methylene chloride, chloroform, ethyl ether, *tert*-butylmethylether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably methylene chloride. This solution of the product can be used just as it is in the following stage of synthesis.

The final compound corresponding to the phase B 5-R'''-2-[[(3-R''-5-R-4-nitro-2-pyridinyl)methyl]thio]-1*H*-benzimidazole of formula (XVI) is obtained by condensation between the 2-chloromethyl-3-R''-5-R-4-nitropyridine of formula (XIV) obtained in the previous stage and the 5-R'''-2-mercaptobenzimidazole of formula (XV), which is available commercially or prepared in advance with usual known procedures described in the bibliography.

This reaction can be carried out under liquid-liquid phase-transfer conditions, using an inorganic base such as sodium hydroxide or potassium hydroxide and a phase transfer catalyst which can belong to the types of quaternary ammonia salts $R_4N^+X^-$, phosphonium salts $R_4P^+X^-$, crown ethers and kryptanes, polyethyleneglycol ethers and

aminoethers, phosphorimides or oxyphosphorated derivatives or sulphoxides, preferably salts of quaternary ammonium such as those of triethylbenzylammonium, tetraethylammonium, tetrabutylammonium, 5 tetraheptylammonium, trioctylmethylammonium (Aliquat 336) while the associated anion can be X⁻ chloride, bromide, iodide, hydrogenosulphate, arseniate, naphthalenosulphonate, preferably triethylbenzylammonium chloride. The process can be carried out at temperatures 10 ranging between 0 and 100°C, preferably between 15-30°C and the reaction time ranges between 1-10 hours. Once the reaction has been completed the product is isolated by concentration and crystallisation from the organic phase.

This same reaction can also be carried out by means of 15 usual techniques in homogeneous phase and non-transfer of phase, using a polar solvent such as water, methanol, ethanol, isopropanol, n-butanol, acetonitrile or methylsobutylketone, in which there is prior formation of the salt of 5-R'''-2-mercaptobenzimidazole of formula (XV) 20 and it is made to react with the 2-Chloromethyl-3-R''-5-R-4-nitropyridine of formula (XIV), which in this case would have been isolated previously by evaporation of the solvent from the solution obtained in the previous phase.

25 Phase C consists in an oxidation reaction of the compound obtained in the previous stage B 5-R'''-2-[(3-R''-5-R-4-nitro-2-pyridinyl)methyl]thio]-1H-benzimidazole of formula (XVI) to provide the corresponding 5-R'''-2- 30 [(3-R''-5-R-4-nitro-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole of formula (XVII). The great advantage of this procedure lies in the fact that this oxidation reaction takes place in the penultimate phase of synthesis, thereby increasing the probability of reducing the proportion of N-oxide and sulphone impurities usual in 35 this type of reactions and reducing their percentage in

the end product final, which must be obtained from this one.

This oxidation can be carried out using various types of reagents already described in the bibliography and commonly used in the oxidation of sulphides to sulphoxides, such as those noted by Madesclaire et al., in Tetrahedron, 42, 5459 (1986), or for example metachloroperbenzoic acid (Uchida et al., Chem. Pharm. Bull., 38, 534, (1990)), sodium metaperyodate (ES 550070), 10 iodosobenzene (ES 539793), oxygenated water with catalysts of vanadium, titanium or molybdenum (EP 302720) or dioxyranes such as potassium peroxymonosulphate or those ketones and this last reagent (ES 2060541). Any of these agents can be used in the oxidation of intermediate 15 sulphides of general formula (XVI) a sulphoxides of general formula (XVII). The authors of this invention have nevertheless found that the oxidising agent whose use presents most advantages and that is thus preferably used is peracetic acid, given that, in addition to being a low- 20 cost product, its use suprisingly gives rise to the formation of very few by-products, which permits isolation of an end sulphoxide with low content of the *N*-oxide and sulphone impurities, probably due to the fact that mixed crystals are not formed. It has also been found that the 25 use of a reaction medium made up of a mixture of a halogenated solvent such as chloroform, methylene chloride, dichloroethane, trichloroethane or carbon tetrachloride and an alcohol such as methanol, ethanol, isopropanol, *n*-propanol, *n*-butanol or *tert*-butanol, 30 preferably methyleno-methanol chloride, largely prevents formation of the impurity sulphone. The process is carried out at temperatures ranging between 0-70°C, preferably between 0-5°C, which also avoids the formation of the aforementioned undesirable impurities. The reaction time 35 varies between 5 minutes and 6 hours after the addition of

the paracetic acid. Once the reaction has finished, the halogenated solvent is evaporated at low pressure and the product is crystallised by cooling, for subsequent filtering and purification.

5 It should be noted that one of the end products obtained in stage C, specifically the 5-methoxy-2-[[[3,5-dimethyl-4-nitro-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazol of general formula (XVII) in which the R and R'' is methyl and R''' is methoxy, are not described in
10 the literature, being now characterised for the first time.

Stage D consists in the nucleophyllic replacement of the "nitro" radical of the compound obtained in prior
15 stage C, 5-R'''-2-[[[3-R''-5-R-4-nitro-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazol of formula (XVII), with the corresponding R'O alkoxide, under certain conditions to prevent decomposition of the end product obtained
20 5-R'''-2-[[[4-R'O-3-R''-5-R-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole of general formula (I).

Surprisingly, the authors of this invention have found that when an attempt is made to carry out this reaction under the usual conditions described in the bibliography to replace a nitro group or a halogen with alcohols such
25 as 3-methoxypropanol in the case of Rabeprazol or 2,2,2-trifluoroethanol to make Lansoprazol, as described for example in Spanish patent application ES 2023609, respectively, decomposition of the product takes place before the reaction is completed.

30 Moreover, the use as a solvent in this type of reaction of the alcohol corresponding to the alkoxide used, such as methanol for making omeprazol, methanol, which is the usual practice described in the bibliography for replacing the nitro group where the sulfoxides are
35 obtained previously, does not provide good results either,

as fast breakdown of the product occurs in addition to undesirable coloration thereof.

This is why the conditions described in patents ES 9901579 and ES 2023609 are not applicable for use thereof in the manufacturing of the compounds of formula (I), and specifically Omeprazol.

It also arises that the reaction occurs very slowly or that decomposition occurs when dimethylformamide or dimethylsulphoxide are used as solvents and the corresponding tocooxide as reagent, in this case sodium methoxide.

Surprisingly, the authors of this invention have discovered that in order to avoid this the reaction has to be carried out in a certain mixture of an aprotic polar solvent, such as dimethylsulphoxide and the alcohol corresponding to the alkoxide used, in this case methanol.

In the new improved procedure of this invention, the reagents and the conditions of temperature, pH, concentration, etc., at which the reaction must be carried out to avoid decomposition of the end product are clearly defined, including the use of ammonium hydroxide, monoethanolamine, triethylamine or other organic base as stabilising agent of the product in solution, which is made up of a mixture of methanol and dimethylsulphoxide.

This substitution reaction is carried out by reaction of the alkaline metal alcoholate $R'OX$, in which $X = Na, K, Li$ with the 5-R'''-2-[[(3-R''-5-R-4-nitro-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazol of formula (XVII) obtained as indicated in stage C in a mixture of the corresponding tocohol $R'OH$ and dimethylsulphoxide. The process takes place at temperatures ranging between ambient temperature and 150°C, preferably between 60-80°C. The reaction solvent is made up of a mixture of the alcohol $R'OH$ and dimethylsulphoxide in various proportions, preferably 1:1 (v:v). The reaction time

varies between 1 and 12 hours, though the reaction normally occurs over 3-6 hours. Once the reaction has ended the reaction mixture is diluted and the pH adjusted between 7,5-8,5 by addition of an acid such as acetic acid or hydrochloric acid, preferably acetic acid. The aqueous phase is then extracted with an organic solvent such as methylene chloride, chloroform, ethyl ether, *tert*-butylmethyl ether, di-isopropyl ether, ethyl acetate, butyl acetate or toluene, preferably ethyl acetate. Finally, this organic phase is washed with water to eliminate the remains of dimethylsulphoxide and methanol, and the solvent dried and finally evaporated at low pressure at a temperature of <40°C. The residue thus obtained is crystallised in an organic solvent, preferably acetonitril, to which has been added a base such as monoethanolamine, triethylamine or ammonium hydroxide in order to ensure stability of the product, and is finally purified by recrystallisation in an organic solvent such as acetonitril, ethyl acetate, methylethylketone, di-isopropyl ether, *tert*-butylmethylether, *N,N*-dimethylformamide, *n*-hexane, toluene, alcohol-water mixtures or methyl or ethyl formate, preferably acetonitril or acetone-water.

Finally, if so wished, the metal salt corresponding to the product is obtained by known traditional procedures, such as dissolution of the product in a mixture of the aqueous hydroxide in ethanol which contains the stoichiometric quantity of said base, evaporation of the solvent at low pressure and crystallisation of the residue with a scanty polar solvent such as *tert*-butylmethyl ether, di-isopropylether, ethyl ether, *n*-hexane, heptane, etc. They can also be obtained by using solely water as solvent and evaporating the resulting solution to dryness.

For preparation of the sodium salt other bases such as sodium carbonate, sodium methoxide and sodium ethoxide in water, methanol or ethanol, respectively, can be used.

To obtain the salt it is also possible to use any inorganic salt which acts as a donor of the corresponding cation, such as chlorides, carbonates, bicarbonates, phosphates, etc.

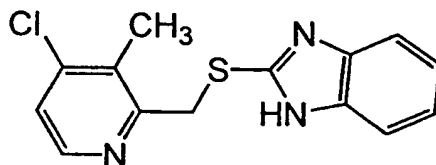
All the conditions set out above for each of the various stages and including obtaining of the various compounds of general formula (III), (IV), (V), (VII), (VIII) and (I), are illustrated by means of the specific examples provided below.

4. EXAMPLES

The following non-restrictive examples illustrate this invention

Example 1

Obtaining 2-[[(4-Chloro-3-methyl-2-pyridinyl)methyl]thio]-1H-benzimidazole



a) Obtaining 2-Acetoxymethyl-4-Chloro-3-methylpyridine

To a solution made up of 95 g of N-oxide of 4-chloro-2,3-dimethylpyridine in 600 ml of toluene, previously heated to 90°C, is added 180 g of acetic anhydride drop by drop and with stirring in such a way that the temperature is kept between 90-105°C. Once the addition is complete, the reaction mixture is kept, with stirring, at 105-110°C for 2 hours. At the end of this time the solvent is

evaporated at low pressure at temperature of $<50^{\circ}\text{C}$ and the residue is used just as it is in the following stage of synthesis.

5 b) Obtaining 4-Chloro-2-hydroxymethyl-3-methylpyridine

To a solution of the residue previously obtained as indicated in stage a) in 250 ml of methanol, previously cooled to between 0 and 5°C , is added another solution made up of 140 g of KOH in 595 ml of H_2O , little by little
10 and with stirring, so that the temperature is kept at $<15^{\circ}\text{C}$. Once the addition is complete, the reaction mixture is kept, with stirring, at $25\text{--}30^{\circ}\text{C}$ for 4 hours, ensuring that the pH value is between 12 and 13 by adding more aqueous KOH if necessary. At the end of this time the
15 methanol is evaporated at low pressure, the resulting aqueous phase is extracted with methylene chloride (4 x 150 ml) and the combined organic extracts are dried over anhydrous Na_2SO_4 . Finally, after filtering the desiccant and concentrating the filtrate to some 300 ml, a solution
20 of the aforesaid product is obtained and can be used just as it is in the following stage of synthesis.

c) Obtaining 4-Chloro-2-chloromethyl-3-methylpyridine

To the solution previously obtained as indicated in
25 stage b) in 250 ml of methanol, previously cooled to between 0 and 5°C , is added 52 g of thionyl chloride in such a way that this same temperature is maintained and the reaction mixture is then kept with stirring under these same conditions for 15 minutes. Then, little by
30 little and with stirring, another solution made up of 60 g of NaOH in 450 ml of H_2O is added in such a way that the temperature is kept at $<20^{\circ}\text{C}$. At the end of the addition the pH of the aqueous phase will have to be between 8.0 and 8.5. Finally, the organic phase is separated, the
35 aqueous phase is extracted with methylene chloride (2 x

100 ml) and the organic extracts are combined and used just as they are in the following stage of synthesis.

d) Obtaining 2-[[[4-Chloro-3-methyl-2-pyridinyl) 5 methyl]thio]-1H-benzimidazole

To an aqueous solution made up of 40 g of NaOH in 400 ml of H₂O, previously cooled to between 10 and 15°C is added 60 g of 2-mercaptobenzimidazole and 12 g of triethylbenzylammonium chloride. The resulting mixture is 10 kept with stirring for 15 minutes and then has added to it the resulting solution obtained as indicated in stage c), little by little and with stirring in such a way that the temperature is kept at <15°C. Once this addition has finished, the reaction mixture is kept with stirring at 15 25-30°C for 2 hours. At the end of that time, some 250 ml of methylene chloride is evaporated at low pressure and the resulting mixture is cooled to between 0 and 5°C and maintained for 1 hour. The indicated product is thus crystallised and finally filtered, washed with H₂O and 20 dried. This process yields 153 g of a light brown solid of the following characteristics:

- Melting point: 157-159°C
- IR spectrum (KBr, \square cm⁻¹): 3350, 3066, 1564, 1439, 1262, 1233, 742
- 25 - ¹H-RMN spectrum (500 MHz, DMSO-D₆, \square ppm): 8,29 (d, J=5,2 Hz, 1H); 7,46-7,44 (m, 3H); 7,11-7,14 (m, 2H); 4,80 (s, 2H); 2,45 (s, 3H).
- Quantitative Ultimate Analysis. Calculated for C₁₄H₁₂ClN₃S

30

	%C	%H	%N
Calcul'd	58.03	4.17	14.50
Found	58.30	4.17	14.72

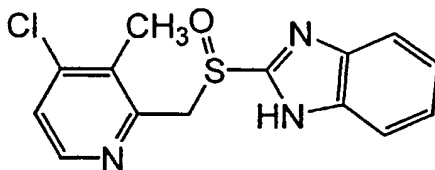
Example 2

Obtaining

2-[[(4-Chloro-3-methyl-2-

pyridinyl)methyl]sulphonyl]-1H-benzimidazole

5



To a solution made up of 40 g of 2-[[(4-chloro-3-methyl-2-pyridinyl)methyl]thio]-1H-benzimidazole obtained as indicated in Example 1, in 600 ml of methylene chloride and 400 ml of isopropanol, previously cooled to between 15 and 25°C, is added slowly and with stirring 30 g of peracetic acid (35% sol.) in such a way that the temperature is maintained within the aforesaid range. When the addition has finished, the methylene chloride is evaporated under vacuum, ensuring that the temperature is always <40°C. The reaction mass is then cooled to between 20-25°C, and to it is added 300 ml of H₂O. The resulting mixture is kept at 0-5°C for at least 1 hour until complete precipitation of the product has been achieved. Finally, the solid thus obtained is filtered, washed with isopropanol/water (1:1) and dried. This provides 39.5 g of a yellowish solid of the following characteristics:

25 - Melting point: 150°C with decomposition

- IR spectrum (KBr, cm^{-1}): 3345, 3065, 1560, 1434, 1407, 1025, 751

- ¹H-RMN spectrum (500 MHz, DMSO-D₆, ppm): 8,25 (d, J=5,2 Hz, 1H); 7,66-7,62 (m, 2H); 7,47 (d, J=5,2 Hz, 1H); 30 7,31-7,29 (m, 2H); 4,88 (s, 2H); 2,36 (s, 3H).

33

- Quantitative Ultimate Analysis. Calculated for $C_{14}H_{12}ClN_3OS$

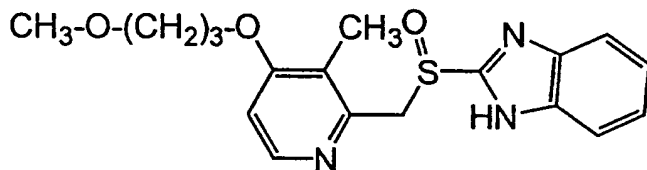
	%C	%H	%N
Calc'd	54.99	3.96	13.74
Found	54.94	4.02	13.37

5

Example 3

Obtaining 2-[[[3-Methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazol (Rabeprazol)

10



To a suspension made up of 3.9 g (97.5 mmol) of sodium hydride 60% in 10 ml of *N,N*-dimethylformamide, previously cooled to 0-5°C, is added 12 g (133.3 mmol) of 3-methoxypropanol, slowly and with stirring, in such a way that the temperature is kept at <15°C. Once the addition has finished, the reaction mixture is kept with stirring, first at 0-15°C for 15 minutes, and then at 40-45°C for 30 minutes. This suspension made up of the sodium salt of the 3-methoxypropanol is then cooled in advance to 5-10°C and to it is added slowly 10 g (32.7 mmol) of 2-[[4-chloro-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole obtained as indicated above in Example 2, in such a way that the temperature is maintained always at <20°C. Once the addition has been completed, the reaction mixture is kept with stirring at 65-70°C for 2 hours. At the end of

this time the resulting mixture is cooled to 5-10°C and 150 ml of water is added little by little and with stirring, in such a way that the temperature is maintained always at <25°C and the pH of the solution is between 12.5 and 13.5. If the pH were to be lower, it would be adjusted to those margins by the addition of a small quantity of NaOH at 50%. The aqueous phase is then washed with methylene chloride (2 x 75 ml), decoloured with active carbon, and to this is added 5 ml of triethylamine and 75 ml of ethyl acetate and the pH adjusted to between 10.8 and 11.0 by the addition of a solution composed of 3 g of acetic acid in 20 ml of H₂O. Afterwards, the resulting organic phase is separated, and to it is added 0.1 g of monethanolamine to stabilise it and the aqueous phase is extracted with ethyl acetate (2 x 75 ml). Finally, said extracts are combined with the prior organic phase and then dried over anhydrous Na₂SO₄. After filtering the desiccant, the filtrate is concentrated to a volume of some 25 ml by evaporation of the solvent at low pressure and at a temperature of <40°C, and the resulting solution is cooled to 0-5°C for at least 4 hours until the product has solidified completely. Finally, the solid obtained thereby is filtered, washed with ethyl acetate and purified by recrystallisation in acetonitrile, to which is added a small quantity of monoethanolamine to ensure product stability. Thus are obtained 9.3 g of a whitish solid of the following characteristics:

- Melting point: 99-100°C
- IR spectrum(KBr, cm^{-1}): 3380, 2933, 1582, 1442, 1299, 1096, 1074, 751
- ¹H-RMN spectrum(500 MHz, DMSO-D₆, ppm): 13,09 (s, 1H, n~); 8,20 (d, J=5,8 Hz, 1H); 7,64 (d.d., J=6,1 and 3,2 Hz, 2H); 7,28 (d.d., J=6,1 and 3,2 Hz, 2H); 6,94 (d, J=5,8 Hz, 1H); 4,78 (d, J=13,45 Hz, 1H); 4,69 (d, J=13,45 Hz, 1H); 4,08 (t, J=6,2 Hz, 2H); 3,46 (t, J=6,2 Hz, 2H); 3,23 (s,

35

3H); 2,12 (s, 3H); 1,98-1,95 (m, 2H).

- Quantitative Ultimate Analysis. Calculated for
C₁₈H₂₁N₃O₃S

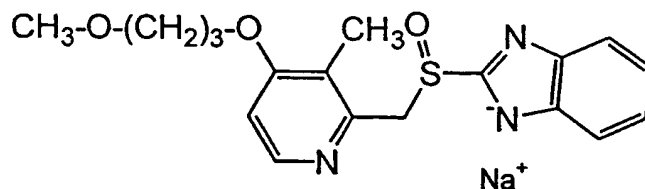
	%C	%H	%N
Calc'd	60.15	5.89	11.69
Found	59.93	5.98	11.52

5

Example 4

Obtaining 2-[[[3-Methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole Sodium Salt (sodium salt of rabeprazole)

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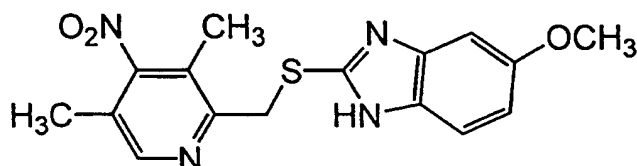


To a solution made up of 0.412 g of NaOH in 100 ml of H₂O is added 3.7 g of 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, obtained as indicated in Example 3, and the resulting mixture is kept with stirring at ambient temperature up till complete dissolution of this last product. Then 200 ml of ethanol is added and the resulting solution is concentrated to dryness at low pressure. Finally, the residue thus obtained is triturated with *tert*-butylmethyl ether, filtered and dried. Thus is obtained with quantitative yield a whitish solid with a melting point of 140-141°C with decomposition.

25

Example 5

Obtaining 5-methoxy-2-[[(4-nitro-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole



5

a) Obtaining 2-acetoxymethyl-4-nitro-3,5-dimethylpyridine

A solution made up of 72 g of 4-nitro-2,3,5-trimethylpyridine N-oxide in 50 ml of acetic acid is added gradually, over some 30 minutes, to 80 ml of acetic anhydride previously heated to 60-65°C, in such a way that the temperature is maintained within said limits. Once the addition is completed, the reaction mixture is maintained with stirring at 70-75°C for 6 hours. At the end of this time 250 ml of water is added, the pH of the resulting mixture is adjusted to between 8,2-8,5 by addition of sodium hydroxide 50% and the product is extracted with methylene chloride (2 x 125 ml). Finally, after evaporating the solvent at low pressure, the residue obtained is dissolved in 200 ml of methanol and this solution is used just as it is in the following stage of synthesis.

b) Obtaining 4-nitro-3,5-dimethyl-2-hydroxymethylpyridine

To a methanolic solution of de 2-acetoxymethyl-4-Nitro-3,5-dimethylpyridine obtained as indicated above in stage a), is added little by little and with stirring at ambient temperature another solution made up of 60 g of sodium methoxide in methanol at 30%. Once the addition is complete the reaction mixture is kept with stirring

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between 20-25°C for 45-60 minutes. At the end of this time, 250 mL of water is added and the product is extracted with methylene chloride (2 x 125 mL). Finally, the product is extracted in hydrochlorate form from this organic phase by treating it with dilute hydrochloric acid and precipitated as a base at a pH of between 7.5-8 by addition of sodium hydroxide 30% following the addition of 100 mL isopropyl alcohol. The product thus obtained is filtered and dried, thus providing 68 g (94% yield) of the compound in the form of a whitish solid which is used just as it is without prior purification in the following stage of synthesis.

c) Obtaining 4-nitro-2-chloromethyl-3,5-dimethylpyridine

To a solution made up of 50 g of 4-nitro-3,5-dimethyl-2-hydroxymethylpyridine obtained as indicated in stage b) in 500 mL of methylene chloride, previously cooled to between 0-5°C, is added little by little and with stirring 24 mL (39 g) of thionyl chloride in such a way that the temperature is kept within that same range of 0-5°C. Once the addition is complete, the reaction mixture is maintained with stirring under these same conditions for 1 hour. Once the reaction has ended, there is added firstly, little by little and with stirring, 130 mL of water and then the pH of the medium is adjusted to 8.0 by the addition of some 55 mL of NaOH 50%. The product is then extracted from the aqueous phase with methylene chloride (2 x 125 mL), the solvent evaporated from the organic extracts to provide a residue which is finally dissolved in 200 mL of methanol, and the resulting solution is used just as it is without prior purification in the following stage of synthesis.

d) Obtaining 5-methoxy-2-[(4-nitro-3,5-dimethyl-2-

pyridinyl)methyl]tio]-1H-benzimidazole

To the above resulting methanolic solution, obtained as indicated in stage c), is added 50 g of 5-methoxy-2-mercaptobenzimidazole and a solution made up of 9 g of NaOH in 70 mL of water. The resulting mixture is then heated under reflux for 1 hour, ensuring at all times that the pH of the medium is between 8.0-9.0. Once the reaction has finished, the resulting mixture is cooled to 5°C and the solid product thus crystallised is filtered, washed with methanol and dried. Thus is obtained 87 g (92% yield) of a whitish-yellow solid of the following characteristics:

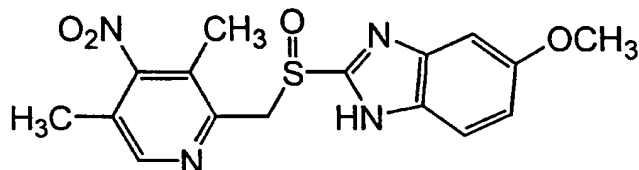
- Melting point: 120-121°C
- 15 - IR spectrum (KBr, cm^{-1}): 3447, 3118, 2955, 1636, 1534, 1429, 1396, 1300, 1274, 1198, 1156, 1029, 818, 738.
- ^1H -RMN spectrum (500 MHz, DMSO- d_6 , δ ppm): 13,21-11,62 (sa, NH); 8,49 (s, 1H); 7,33 (d, $J= 8,8$ Hz, 20 1H); 6,96 (d, $J= 1,5$ Hz, 1H); 6,75 (dd, $J= 8,5$ and 2,4 Hz, 1H); 4,76 (s, 2H); 3,75 (s, 3H); 2,30 (s, 3H); 2,21 (s, 3H).
- Quantitative Ultimate Analysis. Calculated for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_3\text{S} \cdot \text{H}_2\text{O}$

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	%C	%H	%N
Calc'd	53,02	5,01	15,46
Found	52,76	4,98	15,66

Example 6

Obtaining 5-methoxy-2-[[[(4-nitro-3,5-dimethyl-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazole



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To a solution made up of 73 g de 5-methoxy-2-[[[(4-nitro-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole obtained as indicated in Example 1, in 730 mL of methylene chloride and 430 mL de methanol, previously cooled to between 0-5°C, is added slowly and with stirring 45 g of paracetic acid (sol. 36%) in such a way that the temperature remains between those limits. Once the addition is completed, 6 g of sodium thiosulphate dissolved in 80 mL of water is added and the methylene chloride and part of the methanol evaporated until a final volume of some 350 mL is achieved. The reaction mass is then cooled to 5°C for at least one hour until the product has precipitated completely. Finally, the solid thus obtained is filtered and dried. This procedure provides 70 g (92% yield) of a whitish solid of the following characteristics:

- Melting point: 115-116°C
- IR spectrum (KBr, cm^{-1}): 3405, 2942, 1628, 1539, 1458, 1414, 1373, 1207, 1154, 1032, 814, 735.
- ^1H -RMN spectrum (500 MHz, DMSO-d_6 , δ ppm): 13,62-13,05 (sa, NH); 8,49 (s, 1H); 7,53 (d, $J=8,8$ Hz, 1H); 7,08 (s, 1H); 6,91 (dd, $J=8,8$ and 2,4 Hz, 1H); 4,89 (d, $J=13,7$ Hz, 1H); 4,86 (d, $J=13,7$ Hz, 1H); 3,80

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(s, 3H); 2,21 (s, 6H).

- Quantitative Ultimate Analysis. Calculated for $C_{16}H_{16}N_4O_4S \cdot H_2O$

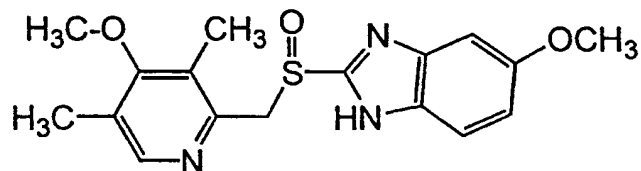
	%C	%H	%N
Calc'd	50.79	4.79	14.81
Found	50.42	4.76	14.42

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Example 7

Obtaining 5-methoxy-2-[[(4-methoxy-3,5-dimethyl)-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazole (Omeprazol)

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To a solution made up of 60 g of 5-methoxy-2-[[(4-nitro-3,5-dimethyl-2-pyridinyl) methyl]sulphonyl]-1H-benzimidazole, obtained as indicated above in Example 2, in 120 mL of dimethylsulphoxide and 120 mL of methanol, is added slowly and with stirring and at ambient temperature 96 g of a 30% solution of sodium methoxide in methanol. Once the addition has finished, the reaction mixture is kept with stirring at 70-75°C for 3-4 hours. At the end of that time, the resulting mixture is cooled to 5-10°C and 250 mL of H_2O added little by little and with stirring, in such a way that the temperature is kept at all times below 25°C and the pH of the solution adjusted to between 7.5-

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8.5 by the addition of acetic acid. The aqueous phase is then extracted with methylene chloride (3 x 100 mL), the combined organic phases are washed with water (2 x 125 mL) and finally the solvent is evaporated at low pressure. 5 Finalmente, the residue obtained is suspended in a mixture of 160 mL of acetonitril and 1 mL of ammonium hydroxide and maintained with stirring between 0-5°C until the product has crystallised completely. Once the product has been filtered, it is purified by recrystallisation in 10 acetone-agua. This provides 49 g (85% yield) of Omeprazol in the form of a white crystalline solid.

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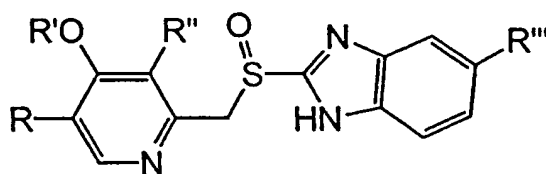
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CLAIMS

- 5 1.- Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphonyl) - 1H-benzimidazole of general formula (I):



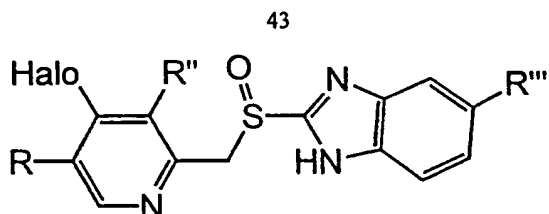
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(I)

including their corresponding metal or quaternary ammonium salts, such as the salts of Li, Na, K, Mg, Ca, Ti, NR₄ (where R is a C₁₋₄-alkyl radical), in which:

- 15 R represents an atom of hydrogen or an alkyl radical such as methyl
 R' represents an alkyl chain, which may or may not be interrupted by an atom of oxygen, such as methyl and 3-methoxypropyl;
 20 R'' represents an alkyl or alkoxy radical such as methyl and methoxy;
 R''' represents an atom of hydrogen or an alkoxy remnant which may or may not be replaced, such as methoxy and difluoromethoxy.
 25 characterised in that it is carried out by substitution of an halogen in position "4" of the pyridine ring of the compounds of of general formula (VIII)

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(VIII)

by an alkoxide in the presence of a base and within an aprotic polar solvent.

10 2.- Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claim 1, characterised in that the polar solvent can be N,N-dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, 15 tetrahydrofuran, diglyme, acetonitrile, pyridine, N-methylpyrrolidone or the triamide of hexamethylphosphoric acid, preferably N,N-dimethylformamide, with a base such as sodium hydride, potassium tert-butoxide, metal sodium, sodium hydroxide, potassium hydroxide or sodium or 20 potassium carbonate or di-isopropylethylamine.

3.- Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 2, characterised in 25 that the solvent used is dimethylformamide and the base is sodium hydride.

4.- Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphanyl) - 1H-benzimidazole of general 30 formula (I), as claimed in Claims 1 to 3, characterised in that the quantity of alkoxide used is in the proportion of

2 to 4 equivalents in relation to the initial halogenated compound of general formula (VIII).

5 5.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 4, characterised in that the process takes place at temperatures between ambient temperature and 120°C, preferably between 40 and 70°C.

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6.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 5, characterised in that the reaction time of the process varies between 1 and 15 24 hours.

7.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 6, characterised in 20 that the pH of the various aqueous phases generated in the course of making the product has to be always >8.

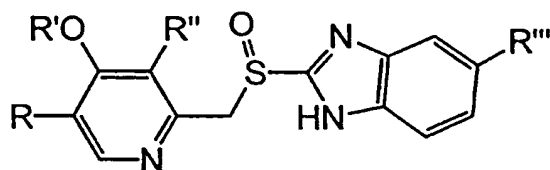
8.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general 25 formula (I), as claimed in Claims 1 to 7, characterised in that monoethanolamine or triethylamine are used as stabilising agent of the organic solutions of said products.

30 9.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 8, characterised in that obtaining of the intermediate compounds of general formula (III), (IV) and (V) takes place without any need 35 to isolate said intermediates.

10.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 8, characterised in
 5 that the making of the intermediate compounds of general formula (VII) is carried out by using phase-transfer conditions in the presence of a phase-transfer catalyst, preferably triethylbenzylammonium chloride.

10 11.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 1 to 8, characterised in that the making of the intermediate compounds of general
 15 formula (VIII) is carried out on the basis of the compounds of general formula (VII) by oxidation with peracetic acid in a mixture of preferably methylene chloride-isopropanol.

12.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general
 20 formula (I):



(I)

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including their corresponding metal or quaternary ammonium salts, such as the salts of Li, Na, K, Mg, Ca, Ti, NR_4 (where R is a C_{1-4} -alkyl radical), in which:

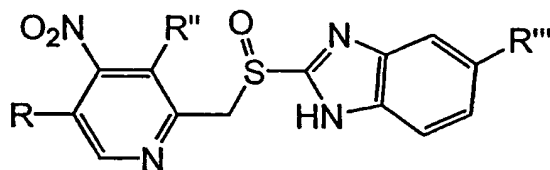
R represents an atom of hydrogen or an alkyl radical such
 30 as methyl;

R' represents an alkyl chain, which may or may not be interrupted by an atom of oxygen, such as methyl and 3-methoxypropyl;

R'' represents an alkyl or alkoxy radical such as methyl and methoxy;

R''' represents an atom of hydrogen or an alkoxy remnant which may or may not be replaced, such as methoxy and difluoromethoxy.

characterised in that it is carried out by replacement of a "nitro" group in position "4" of the pyridine ring of the compounds of the compounds of formula (XVII)



(XVII)

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by an alkoxide radical $R'O^-$ in the presence of a base and within a mixture of solvents made up of the corresponding to alcohol $R'OH$ and another aprotic polar solvent.

13.- Procedure for obtaining derivatives of 2-(2-pyridinylmethylsulphonyl) - 1H-benzimidazole of general formula (I), as claimed in Claim 12, characterised in that the aprotic polar solvent can be *N,N*-dimethylformamide, dimethylsulphoxide, dioxane, methylethylketone, tetrahydrofuran, diglyme, acetonitrile, pyridine, toluene, *N*-methylpyrrolidone or the triamide of hexamethylphosphoric acid, preferably dimethylsulphoxide with a base such as sodium hydride, potassium *tert*-Butoxide, metallic sodium, sodium hydroxide, potassium hydroxide or sodium or potassium

carbonate or di-isopropylethylamine.

14.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 or 13, characterised in that the solvent used in the reaction is a mixture of R'OH-dimethylsulphoxide in proportion (1:1) and in a ratio of 2:1 (v/p) with respect to the initial nitrated compound of formula (XVII).

10

15.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 14, characterised in that the quantity of alkoxide used as a reagent is in the equivalent proportion of 2 to 4 in relation to the initial nitrated compound of formula (XVII).

16.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 a 15, characterised in that the process takes place at temperatures ranging between ambient temperature and 120°C, preferably between 70 and 75°C.

17.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 16, characterised in that the reaction time of the process can vary between 1 and 24 hours, normally taking place over the course of 3-4 hours.

18.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 17, characterised in that the pH of the various aqueous phases generated in

the course of making the product must at all times be >7.5.

19.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 18, characterised in that monoethanolamine, triethylamine or ammonium hydroxide are used, preferably the last, as a stabilising agent for the the product or its solutions.

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20.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 19, characterised in that obtaining of the intermediate compounds of general formula (X), (XI), (XII) and (XIV) takes place without any need to isolate said intermediates.

21.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 20, characterised in that obtaining of the intermediate compounds of general formula (XVI) is carried out using phase-transfer conditions in the presence of a phase-transfer catalyst, preferably quaternary ammonium salts.

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22.- Procedure for obtaining derivatives of 2-(2-pyridinilmethylsulphanyl) - 1H-benzimidazole of general formula (I), as claimed in Claims 12 to 21, characterised in that obtaining of the intermediate compounds of general formula (XVII) is carried out on the basis of the compounds of general formula (XVI) by oxidation with paracetic acid preferably in a mixture of methylene chloride-methanol.

35 23.- Procedure for obtaining derivatives of 2-(2-

pyridinilmethylsulphonyl) - 1H-benzimidazole of general formula (I), as claimed in any of the previous claims, characterised in that it further includes the formation of their metallic or quaternary ammonium salts, by making the
5 "acid form" (I) react with the hydroxide or the donor salt of the corresponding cation in an aqueous or water-alcohol medium.

24.- Procedure for obtaining derivatives of 2-(2-
10 pyridinilmethylsulphonyl) - 1H-benzimidazole of general formula (I), as claimed in any of the previous claims, characterised in that the product obtained by this procedure is Rabeprazol or Pariprazol (R and $R''' = H$, $R' = CH_3-O-(CH_2)_3-$ and $R'' = -CH_3$), of chemical name 2-[[[(4-(3-
15 Methoxypropoxy)-3-methyl-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazole.

25.- Procedure for obtaining derivatives of 2-(2-
pyridinilmethylsulphonyl) - 1H-benzimidazole of general
20 formula (I), as claimed in any of the previous claims, characterised in that the product obtained by this procedure is Omeprazol ($R=R'=R'' = -CH_3$ and $R''' = -O-CH_3$), of chemical name 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazol.

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26.- Procedure for obtaining derivatives of 2-(2-
pyridinilmethylsulphonyl) - 1H-benzimidazole of general formula (I), as claimed in any of the previous claims, characterised in that the product obtained by this
30 procedure is Pantoprazol ($R = H$, $R' = -CH_3$, $R'' = -O-CH_3$ and $R''' = CF_2O-$), of chemical name 5-Difluoromethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazole.

35 27.- A compound of general formula (XVII).

28.-A compound as claimed in Claim 27, where said compound is 5-methoxy-2-[[(4-Nitro-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole.

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29.- Use of a compound of formula (XVII) in the preparation of derivatives of 2-(2-pyridinylmethylsulphinyl)-1*H*-benzimidazole of general formula (I).

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 00/00927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ES 2 037 608 A (TECHQUIN ETABLISSEMENT) 16 June 1993 (1993-06-16) cited in the application claims 1-5; examples 1-3 ---	1-29
Y	ES 2 037 609 A (TECHQUIN ETABLISSEMENT) 16 September 1993 (1993-09-16) cited in the application claims 1-5; examples 1-3 ---	1-29
Y	M. MITTELBACH ET AL.: "Synthesis of 4-Methoxy-2,3,5-trimethylpyridine: a Specific Building Block for Compounds with Gastric-acid Inhibiting Activity" ACTA CHEM. SCAND. SER. B, vol. 42, no. 8, 1988, pages 524-529, XP000940585 page 528, left-hand column --- -/--	1-29



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

25 September 2000

Date of mailing of the international search report

11/10/2000

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Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 00/00927

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE WPI Week 199501 Derwent Publications Ltd., London, GB; AN 1995-001226 XP002148274 & ES 2 060 541 A (VINAS LAB), 16 November 1994 (1994-11-16) cited in the application abstract</p>	1-29
Y	<p>C. O. KAPPE, T. KAPPE: "Synthesis of Substituted 3-Pyridinecarbonitriles with Potential Biological Activity" MONATSHFTE CHEMIE, vol. 120, no. 12, 1989, pages 1095-1100, XP000940556 page 1099</p>	1-29
Y	<p>A. MICHAELIS, R. HANISCH: "Ueber den 2.6-Dimethyl-4-Chlor-Nicotinsäureäthyleste r" CHEMISCHE BERICHTE, vol. 35, 1902, pages 3156-3161, XP000940584 page 3160</p>	1-29
Y	<p>N. SPERBER ET AL.: "Parasympathetic Blocking Agents. III. N-Alkylpiperidinecarboxylic Esters" J. AMER. CHEM. SOC., vol. 81, 1959, pages 704-709, XP000940555 page 708, right-hand column</p>	1-29
Y	<p>DATABASE WPI Week 199208 Derwent Publications Ltd., London, GB; AN 1992-058738 XP002148275 & ES 2 023 609 A (INKE SA), 16 January 1992 (1992-01-16) cited in the application abstract</p>	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/00927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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ES 2037609 A	01-04-1994	NONE	
ES 2060541 A	16-11-1994	NONE	
ES 2023609 A	16-01-1992	NONE	